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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/584,586	05/31/2000	Brian Sorrentino	1340-1-021CIP	4632

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EXAMINER
SORBELLO, ELEANOR

ART UNIT	PAPER NUMBER
1632	11

DATE MAILED: 03/28/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/584,586	Applicant(s) SORRENTINO ET AL.	
	Examiner Eleanor Sorbello	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If the period for reply specified above is the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *16-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7*.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-15 in Paper No. 10 is acknowledged. The traversal is on the ground(s) that Group I and II are not "distinct" because there is a relationship between the two groups and furthermore they are have the same classification, and will only require the same search. This is not found persuasive because Group I is directed to ex-vivo expansion which does not require considerations that would be necessary in the examination of Group II which requires in vivo administration of gene modified cells. The considerations that are required for in vivo administration are entirely distinct due to numerous other complicating factors of the in vivo environment that would influence the administered cells, unlike the ex vivo cultured cells. This will therefore require a different search.

2. The product claims, claims 14 and 15 will be examined with the elected group, Group I.

3. The requirement is still deemed proper and is therefore made FINAL.

4. Claims 16-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-11, 13-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a (i) method of performing ex vivo expansion of (a) a murine HSC comprising transducing the murine HSC with a nucleic acid encoding any ABC transporter and (b) a human HSC comprising transducing the human HSC with any ABC transporter for a period upto 3 days, **does not** reasonably provide enablement for a method of performing ex vivo expansion of any HSC for instance human HSC comprising transducing the human HSC with any ABC promoter using any vector and culturing the gene modified human HSC so as to expand the modified human HSC for at least 9 days. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to ex vivo methods for expansion of any HSC that has been modified previously with a gene via vectors carrying the gene of interest. The claims also encompass any HSC that has been modified previously with a gene via vectors carrying the gene of interest, and expanded for at least 9 days.

The state of the art with regards gene transfer into human HSC with retroviral vectors has been very low in contrast to the much higher efficiency observed in murine experiments. This statement was made by Hanazono et al. in a Concise Review on

Stem Cells, in Stem Cells 2001: 19: 12-23. They state that the quiescent nature of human HSCs, and the lower density of retroviral receptors on them hindered the efficient gene transfer with retroviral vectors. They also stated that non-human primates are markedly similar to humans in all aspects including the HSC biology, their models are considered to be important to evaluate and improve gene transfer into human HSCs. They state that to date numerous vectors have been used to transfect human HSC, such as adenoviral vectors, AAVs, lentiviral vectors etc. However, they state that the adenoviral vectors and AAVs do not seem appropriate for applications such as these which require long-term expression of transgenes in HSCs since those vectors do not integrate into the genome. (see abstract and pages 12, 13 col. 1).

Applicants claim transfecting and expanding any HSC with any gene and subsequently expanding the transfected HSC for at least a period of 9 days. It is not clear from the experimentation provided that the HSCs that applicants were transfecting with retroviral vectors were actually human HSCs. Applicants have shown a 100 fold expansion of HSC modified by a gene encoding MDR and DHFR, in Figure 1A and 1B. However, applicants have not stated that these gene modified HSCs were specifically human, and that they were not murine HSCs.

Because the prior art does not teach one how to transduce human HSCs with a gene and be assured of success with any and all viral vectors and be able to expand these cells in culture so as to grow them for extended periods of time to a high degree such as 100 fold, the guidance in the specification should be very precise so that one of skill in the art will not require undue experimentation to make and use the instant

invention as claimed. However, the teachings in the specification with regard to the conditions that gave rise to this degree of expansion appears sparse. Therefore, it is not clear that one of skill in the art will be able to reproduce this dramatic increase in gene modified human HSC in culture without undue experimentation.

Therefore, in view of the breadth of the claims, state of the art and guidance in the specification it is not clear that one of skill in the art will be able to make and use the instant invention without undue experimentation.

In view of this, it would prove an arduous task for one skilled in the art to be able to practice the claimed invention of transfecting human HSCs with a gene and expanding these cells for a minimum of 9 days. Hence, since one skilled in the art cannot readily anticipate the results predicted within the subject matter to which the claimed invention pertains, then there is a lack of predictability in the art.

In conclusion, given the nature of the invention, the state of the art, the demonstrated lack of predictability of the art, the amount of guidance set forth, the breadth of the claims, one of skill in the art could not make and use the invention without undue experimentation.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 recites the limitation "The method of claim 1 wherein the cytokine". Claim 1 bears no reference to a cytokine. Therefore, there is insufficient antecedent basis for this limitation in claim 4.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

9. Claims 1-12, 14 are rejected under 35 U.S.C. 102(b) as being anticipated by McDonagh, K. (W/O 93/24613). (See discussion below).

10. Claims 1-12, 14 are rejected under 35 U.S.C. 102 (e) as being anticipated by McDonagh, K. (U.S. Pat. NO: 5,837,536).

The base claim is directed to a method for performing ex vivo expansion (or cell culture) of HSC with a gene encoding an ABC transporter and the subsequent expansion of the HSC comprising the ABC transporter. McDonagh teach the embodiments of the base claim and further limitations encompassed by the claims as discussed below.

McDonagh et al. teach ex vivo expansion of HSC comprising a MDR1 gene that is expanded 10 fold in 72 hours. (see U.S. Pat. col 15, line 31). McDonagh et al. teaches expansion in the presence of a cytokine such as interleukin-3 and interleukin 6. (see U.S. Pat. col. 15, line 17). McDonagh et al. also teach a DNA sequence for a human mdr1 gene which encodes p-glycoprotein, wherein at least one base in a splice region of the DNA encoding the p-glycoprotein is changed such that no truncation of the p-glycoprotein occurs upon expression. (see abstract). McDonagh teach retroviral vectors, such as a Harvey Murine Sarcoma vector; adenoviral vectors and AAVs for use in the method of transducing a HSC. (see U.S. Pat. col. 3, lines 43-67). McDonagh et al. also refer to prior art teachings wherein retroviral vectors are used to transfer and express mdr1 gene in murine hematopoietic cells. (see U.S Pat. col. 6, lines 48-65). McDonagh et al. also anticipates that primate cells (HSC) may be genetically engineered, and in particular for applications for the use of repopulating primate HSCs which are genetically engineered with DNA encoding MDR. (see U.S. Pat. col. 7, lines 5-20).

Therefore, McDonagh anticipates all limitations encompassed by the rejected claims.

Conclusion

11. Claims 1-15 are rejected.

12. Any inquiry concerning this communication should be directed to Eleanor Sorbello, who can be reached at (703)-308-6043. The examiner can normally be reached on Mondays-Fridays from 6.30 a.m. to 3.00 p.m. EST.

Questions of formal matters can be directed to the patent analyst, Patsy Zimmerman, whose telephone number is (703) 308-0009.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

If the claims are amended canceled and/or added the applicants are required to follow Amendment Practice under 37 CFR § 1.121 *(http://www.uspto.gov)* and A CLEAN COPY OF **ALL** PENDING CLAIMS IS REQUESTED to facilitate further examination.

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